Critical Digest.

ON MULTIPLE SCLEROSIS, WITH ESPECIAL REFERENCE TO ITS CLINICAL SYMPTOMS, ITS ETIOLOGY AND PATHOLOGY.

By B. SACHS, M.D.

(*Concluded.*)

ETIOLOGY.

Opinions have varied much regarding the cause or causes of multiple sclerosis. At the very outset, it will be well to enter a protest against the supposition that the disease, occurring at widely different periods of life, should or could be due to one cause only. But, strangely enough, whenever any data are collected in favor of proving the existence of some special etiological factor, that special factor, in the minds of many, becomes the sole cause of the disease. The study of the subject has led the present writer to the belief that there are several and equally important causes which may give rise to multiple sclerosis. Charcot and his immediate followers recognized the importance of exposure to cold and wet. In recent years little evidence has been brought forward—if we except a contribution by Krafft-Ebing—to substantiate this doctrine; but we may well concede that occasionally it is the refrigeration process, and not a mere wetting, which may be the cause of the disease. The same school attributed multiple sclerosis to traumatism and emotional depression. Mendel has adduced further proof that the disease is at times due to traumatism, basing his views upon four cases of his own and a collection of 24 others taken from literature. It will be remembered that of late years several authors have also contended for the traumatic origin of tabes. Mendel concedes that there must be an acquired or congenital predisposition to the disease, without which the injury would not have led to the development of this widespread morbid process.

Of the value of emotional origin I have seen several illustrations, one being the case of a young girl of 18, who developed typical multiple sclerosis after the death of a parent, and the other, a boy of 12, who was seriously frightened by a fire occurring near his dwelling, and within a few weeks developed the typical symptoms of the disease.

The earliest writers have recognized that disseminated sclerosis, in contradistinction to paralysis agitans, is a disease of early life, the majority of cases occurring before the age of 30, and some of them before the age of puberty. During the past ten years much has been made of the occurrence of the disease in children; but, as we have seen in the preceding section of this paper, the majority of cases should be looked upon with some reserve, though I am not inclined to deny that the disease does occur, however rare it may be. Women were supposed to be subject to the disease more frequently than men. In 39 cases collected by Berlin, 26 were women and 13 men. Such differences may have been accidental, for later statistics have shown a very different relationship between the sexes. In Nolda's collection of 36 cases, occurring in early life, 16 were boys and 10 girls. In Krafft-Ebing's collection there were 58 males and 42 females. In Redlich's experience the number was almost equally divided between men and women—12 males and 11 females. In Stieglitz's statistics there were 17 males and 17 females, the sex of one case not being mentioned. In the 15 cases seen by myself the ordinary division has been entirely reversed, for of these, 10 were males and only 5 females. Such smaller statistics are subject, however, to accidental variations, and it would not be fair to infer from them that the disease shows any distinct preference for sex.

Of late years the occurrence of multiple sclerosis after infectious diseases in early life has led to the theory of its infectious origin. As long ago as 1878, Leyden insisted upon the importance of preceding infectious diseases. Other authors referred to its occurrence after typhoid fever (Ebstein, Kahler, Pick, Westphal and others); after cholera (Joffroy); after smallpox (Charcot); but Marie has been the warmest advocate of the theory of the infectious origin of multiple sclerosis, and he contended more particularly that the primary change was to be looked for in disease of the blood vessels. According to Redlich, who has gone over this part of the subject very thoroughly, up to the year of 1897 cases in support of this view were cited by Schoenfeld (after diphtheria), by Massolongo (after influenza), by Rolland (after phlegmonous angina), by Williamson (after rheumatism), by Torti and Angelini (after malaria). Redlich cites a case of polyneuritis, in a boy of 17, coming on after a sore throat. The clinical symptoms in this case gradually passed into those of multiple sclerosis. Henschen refers to a case of a girl of 14, who developed the symptoms of multiple neuritis after diphtheria, death ensuing after three months. At the autopsy he found multiple sclerosis and degeneration in the peripheral nerves. This case appears to us to need careful interpretation, for it is, at least, questionable whether or not multiple sclerosis existed for some time before the diphtheria. The rapid development and early death make the case an entirely exceptional one.[2]

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[2] While this digest was passing through the press an article by Jürgens has reached the writer. In this communication (Berliner kl. Wochenschrift, April 4, 1898) the author reports upon the case of a child, six months old, that had had convulsions at the age of three months; repeated convulsions with paralysis of right arm. Child died in convulsions. Whatever else the case may have been (instrumental delivery, etc.!) it was surely not a case of multiple sclerosis. The brain contained "sclerotic patches," in which protozoa were found similar to those found in patches in the heart. The finding is of interest. A pity it is that it has no bearing upon multiple sclerosis.

Among more recent authors, Oppenheim, Leyden, Goldscheider and Sachs have favored the occasional infectious origin of the disease, but do not feel warranted in supposing this etiological factor to be far more important than many others. Marie's views have been opposed more particularly by Redlich and Krafft-Ebing. In the 15 cases observed by the present writer only 2 came on after infectious diseases, and in both of these so long after such a disease that a direct relation, as of cause and effect, could not be established. It is well to bear in mind, however, that if infectious diseases were the chief cause of multiple sclerosis, the vast majority of cases should come on before the age of 15, and such is not the case.

Oppenheim has directed attention to the large number of cases of multiple sclerosis in which chronic metallic poisoning seemed to play a rather important part, basing his views upon the frequent occurrence of multiple sclerosis in those who work in factories in which toxic chemical substances are used—such as lead, tin, aniline dyes, and the like. It was Oppenheim, too, who referred to the importance of a puerperal condition as a predisposing cause.

It may be asserted with some degree of assurance that syphilis is not an important etiological factor, although Jacobson, Moncorvo and Filatow have cited cases in which hereditary syphilis was present, and some others (Michaelow and Schuster) have referred to acquired syphilis; but Redlich is correct in issuing a caution, which the present writer has also uttered, that multiple sclerosis and multiple cerebro-spinal syphilis have so many symptoms in common that the differential diagnosis is not easily established. Whether or not the disease be distinctly hereditary is still in doubt, although Eichhorst has published two cases in which the disease occurred in mother and child. Its occurrence as a family disease has been noted by Friedreich and Erb (according to Krafft-Ebing and Redlich), and Totzke has mentioned the occurrence of the disease in two members of the same family. But the question naturally arises, since these cases were not substantiated, whether they may not have been cases of hereditary spastic paralysis.

The latest contribution to this subject has been made by Blumenreich and Jacoby, who report on 29 cases of multiple sclerosis—23 in males and 6 in females—and in these cases the infectious diseases, intoxications and traumatism have been the chief etiological factors. They are of the opinion that the original cause may have preceded the outbreak of the disease for many years, and that the disease may even be of congenital origin. It is somewhat surprising to find that alcoholic and sexual excesses are not cited as occasional etiological factors of some importance; for, in the present writer's experience, two cases seemed to be the result of previous alcoholic excess, and in three now under observation no other factor except prolonged sexual excesses can be found. In these three cases, moreover, the clinical symptoms are so typical that there can be no doubt of the existence of multiple sclerosis.

A little reflection regarding the etiology of multiple sclerosis necessarily leads to the conclusion that many different causes may be at work resulting in the development of the disease, provided there be a predisposition to the disease. I cannot agree with Redlich in refuting Strümpell's theory of the endogenous character of multiple sclerosis, and am inclined to think that for a large number of cases, particularly for those occurring early in life, some slight defect in the original development of the central nervous system must be held responsible for the outbreak of the disease, and that the other etiological factors so frequently referred to are to be regarded as the exciting causes. If we adopt this view, the usual resemblance between the cases of multiple sclerosis developing early in life, and the various forms of hereditary and family affections observed at that period, can be interpreted more readily.

I have also had occasion to observe several cases in which a distinct neurasthenic condition, due to overwork, preceded the development of the symptoms of multiple sclerosis. According to Eddinger's theory,[1] the development of a sclerosis following upon functional exhaustion does not appear to be at all anomalous. And, finally, I may refer to the fact that in one patient of mine, a music teacher, a functional tremor first appeared in the right hand; this was followed by a distinct intention tremor, and from this stage the symptoms passed into those of a typical paralysis agitans. Altogether, the relation of functional to organic nervous diseases would appear to need further attention, for the same sequence of events has no doubt been observed by others, and it is not to be supposed that the diagnosis of a preceding functional condition was erroneously made. Some of the mooted points regarding the etiology of multiple sclerosis acquire additional interest, if we consider them in connection with a discussion of the morbid anatomy and pathogenesis of the disease.

PATHOLOGICAL ANATOMY AND PATHOGENESIS.

The irregular sclerotic patches (plaques) occurring in different parts of the central nervous system constitute the chief anatomical feature of the disease. These "plaques" represent the terminal condition of a morbid process often lasting through a period of years; but a study of "late stages" has helped us as little toward an understanding of the morbid anatomy of multiple sclerosis, as has been the case in regard to poliomyelitis. The process can be understood only, if studied in its earliest stages. Such studies have been made by Ribbert, Cramer, Bikeles, Taylor and Goldscheider.

With some slight exception, the general agreement has been reached that the blood vessels play an important part in the initial stages of the disease. Goldscheider describes the conditions as presented by a patch in the cervical portion of the spinal cord. The blood vessels are dilated, and the adventitia is infiltrated with small cells and with considerable detritus. In the vicinity of these blood vessels the nerve fibres are swollen, the sheath and the axis-cylinder participating in the swelling. The medullary sheath suffers more than the axis-cylinder; at least, every cross-section exhibits a number of naked and well-preserved axis-cylinders. Goldscheider supposes that the enlarged nerve fibres crowd against each other, causing the disintegration and absorption of the myelin of some fibres, thus leaving room for other fibres to persist in their enlarged (swollen) condition. The changes thus far described are not unlike those occurring in an ordinary acute myelitis.

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[1] This theory appears to have received experimental proof; c.f., Report of the Congress f. innere Med., Wiesbaden, 1898.

Taylor is of the opinion that we are not warranted in connecting the vascular changes directly with the sclerotic process, for the patches are not always related to the diseased vessels, and in many plaques the blood vessels are entirely normal, and other portions of the vascular system show no tendency to disease.

As early as 1863 Rindfleisch maintained the importance of disease of the blood vessels. According to him, each plaque contained in its centre a blood vessel with changed walls, denoting a condition of chronic inflammation. Borst found marked changes in almost every blood vessel (hyaline degeneration, narrowing, thickening of the walls, etc.). He also found a condition of hyperlymphosis and lymphstasis, which he supposed caused a destruction of the medullary sheaths; but his views lack support. Redlich found changes in the larger blood vessels, and even in the capillaries; the neuroglia tissue is easily affected in the immediate vicinity of the blood vessels, leading at times to a perivascular sclerosis. Ribbert found in two blood vessels thrombi consisting of leucocytes. A plugging of blood vessels was also noticed by Redlich; but these findings appear to us to have no especial significance, except that they prove that the vascular system is diseased in some instances. It is to be inferred, from other reports, that the blood vessels often remain entirely normal. The impartial inference necessarily to be drawn is that, while the blood vessel may be the starting point of the morbid process in some cases, it need not be so in all, and we shall find, as we proceed in this discussion, that the terminal findings are the only ones that are entirely similar in all cases, but that there is a difference of opinion as to the intermediate stages by which this terminal condition is reached. Thus, in Goldscheider's case the nerve fibres were the structures particularly affected; while in Ribbert's case the neuroglia cells were chiefly affected, and there was no swelling of the nerve fibres.

If the nerve fibre becomes involved, it is no doubt true, as was recognized by the earliest investigators (Rindfleisch, Charcot, Leyden, Schultze) that the medullary sheath is easily destroyed, while the axis-cylinder remains normal. Popoff alone contends that the axis-cylinder is also destroyed, but that it is regenerated. This *may* occur at rare intervals; it is much more rational to assume that the axis-cylinder is not destroyed, and the preservation of normal axis-cylinders in a mass, exhibiting any number of disintegrating medullary sheaths, argues in favor of this view. The preservation of the axis-cylinder is responsible for the lack of secondary degeneration in multiple sclerosis. Buss has recorded an ascending degeneration of the columns of Goll, and of the direct cerebellar tract from the eighth cervical segment into the medulla oblongata. These observations are quite unique, and need further corroboration.

It has been assumed by Redlich and others that the fine fibrils which Popoff took to be regenerated axis-cylinders are part of the proliferating neuroglia tissues. It is also significant that Weigert, whose opinion is of the highest value in this matter, insists that the proliferation of neuroglia tissue is more marked in multiple sclerosis than in any other disease. This statement militates against the view of Lapinsky, that the fine fibrils discovered in the plaques are connective tissue formations issuing from the medullary sheaths, and are not neuroglia fibres. Recent investigations, utilizing Weigert's neuroglia stain, have satisfied Redlich that the proliferating interstitial tissue consists of neuroglia fibres of varying sizes. Huber concedes that there are slight changes in the neuroglia, but that these consist chiefly of lacunæ, due to the loss of nerve fibres, and of the presence of detritus and granular cells. According to Huber, the process is of parenchymatous origin, the changes in the neuroglia and in the blood vessels being secondary. Adamkiewicz has also advocated the theory of the primary affection of nerve fibres.

If the neuroglia be affected, primarily or secondarily, its cells, as well as its fibres, undergo proliferation. Redlich, who has studied this tissue carefully, maintains that the neuroglia changes may be exhibited in various ways: 1. The increase is largely due to the increase of neuroglia fibres, which gradually form a network of fibres, in which only slightly altered nerve fibres will be found. As these neuroglia fibres grow broader and broader, the network becomes denser. 2. In some patches the network is not so dense, the neuroglia cells and their processes being the most pronounced features, while the nerve fibres have dropped out. This appearance is entirely similar to the account given by Huber, to which we have referred above.

Fuerstner is of the opinion[1] that the neuroglia cells are developed from leucocytes, thus bridging over the chasm between those who maintain that the disease is a parenchymatous affection and those who believe it to be of vascular origin. The actual participation of the neuroglia tissue has acquired greater interest, in view of Struempell's recent theory that the disease is due to a primary proliferation of the neuroglia, that multiple sclerosis is practically a multiple gliosis, and that it belongs to the order of endogenous affections which are excited by accidental causes, such as injuries and infectious diseases. Ziegler appears to have entertained a similar view (Redlich).

To complete the record of histological changes, we may add that Gowers referred to the involvement of the ganglion cells in the earlier stages of the disease; while Taylor states very positively that the ganglion cells do not become affected until the late stages of the disease have been reached. He draws this inference from the conditions as observed in three cases of his own. The changes as described by Taylor are: Considerable pigmentation, filling up the entire cell body, which is unusual in healthy young individuals; the nuclei are generally wanting; the nerve processes are well preserved; a diminution of cells. Koeppen found the ganglion cells normal. Obersteiner allowed that "the ganglion cells . . . . may exhibit changes similar to those found in myelitis." (Quoted after Taylor.)

The patches of disseminated sclerosis present a bluish-gray appearance, and are sometimes slightly elevated; at other times the parts in which they occur appear shrunken and contracted. The question has arisen whether there is any rule governing the distribution of the plaques. By some it was supposed that the brain or the spinal cord may be affected singly. Charcot supported the view of a spinal form of multiple sclerosis. Erb accepted this on clinical grounds only. Charcot, Struempell, Erb and many other writers considered that the white substance of the brain and spinal cord was the favored site; that the gray matter was rarely involved. Charcot believed that the cortex of the brain and cerebellum is rarely affected, and it cannot be denied that in this form the statement is true enough. Basing his conclusions upon three cases, Taylor finds: 1. White and gray are affected without distinction. 2. There is no especially favored site for the development of the sclerotic foci. 3. The cortex of the cerebrum and of the cerebellum is not exempt. The points 1 and 2 cannot be accepted unconditionally, as such statements must rest upon the examination of a larger number of cases. Charcot believed that the auditory, the olfactory and the optic nerves are the only cranial nerves affected; others (Cruveilhier, Skoda, Taylor) have found all, or almost all, involved. It is well known that the motor and sensory roots of the spinal nerves are often diseased, and Taylor has demonstrated the occurrence of a marked degeneration of the nerve fibres in the cauda equina.

The sclerotic patches *may* occur anywhere, but there can be little doubt that they *do* occur most frequently in the dorsal half of the pons, of the medulla oblongata (whence the occurrence of "bulbar forms"), in the white strands near the periphery of the cord and in the gray matter near the central canal. Obersteiner believes that the patches are lessened in number as we approach the lumbar portion of the cord. Leyden and Goldscheider describe a condition of diffuse sclerosis, or of a diffuse chronic myelitis, due to the confluence of numerous foci in the spinal cord. These authors also describe a purely spinal form of multiple sclerosis, which is the representative of the old-time chronic myelitis.

The sclerotic patches appear, on macroscopical examination, to be sharply differentiated from the surrounding healthy tissue, but, microscopically, the transition is a gradual one. Taylor has shown, however, that the division between healthy and diseased tissue may be strictly defined, and the same is true in Goldscheider's case. (See Fig. 2 of his article.)

The pathogenesis of multiple sclerosis is still obscure. There are theories enough, but none that explains satisfactorily all the cases. In all probability there is no single mode of origin.

Charcot believed that the disease was due to an interstitial inflammation, with a special proliferation of the neuroglia, the destruction of the parenchyma being secondary to this. Charcot ascribed some importance to the blood vessels, and regarded them as a source of irritation, thus following, in the main, Rindfleisch's teachings. But the part played by the blood vessels did not attain to its present dignity until Marie published his views regarding the infectious origin of disseminated sclerosis, for he supposed that the exciting agents were carried through and along the blood vessels. Ribbert also favored the theory that the plaques were due to some noxious substances conveyed by the blood, and setting up circumscribed inflammatory lesions in different parts of the central nervous system. Mendel explained the traumatic etiology of some cases through the agency of blood vessels. Fuerstner brought the blood vessels into play by making them primarily responsible for nutritive disturbances in the nerve cells and fibres. Goldscheider says: "I believe I shall describe the nature of the morbid process most correctly by assuming the existence of a perivascular inflammation which injures the neighboring nerve structures, causing more especially a disintegration of the medullary sheath, but allowing the axis-cylinder to escape. Later on, in the course of the disease, a reactive interstitial proliferation is established." He regards multiple sclerosis as a form of disseminated myelitis. Koeppen, Huber and Taylor do not attach so much importance to the blood vessels, and Redlich is not convinced that the disease is always of inflammatory origin.

The vascular theory has been opposed by others. Adamkiewicz regards the disease as a parenchymatous degeneration. Weigert is inclined to the belief that the neuroglia changes are secondary to the affections of the parenchyma, and Strümpell, as we have seen, is inclined to regard the disease as being due, primarily, to a peculiar defective (?) development of the neuroglia, which is made evident in later years by especial exciting causes.

We hope soon to be able to shed some further light upon this controversy by researches of our own, but an impartial review of the results published by other authors leads to the conclusion that there is some truth in several of the views advanced. We believe that the vascular theory holds good, particularly for the cases developed after infectious diseases, after injuries, etc.; and, according to the intensity of the toxic agent, the nerve fibres or the neuroglia may be attacked first. This is in agreement with views expressed by Redlich. Congenital anomalies (Ziegler, Struempell) may make the central nervous system an easier prey for the various toxic agencies and other injuries. But there still remains a considerable number of cases which cannot be explained on the supposition of an inflammatory, toxic or traumatic origin, nor as the result of congenital anomalies. These would seem to depend rather upon functional exhaustion, and such exhaustion might affect primarily the nerve elements of the central nervous system. For such cases the assumption of a parenchymatous affection would be most plausible. In spite of the numerous contributions to this subject, further investigation, impartially conducted, will be beneficial. Above all, there is need of careful inquiries into the earliest histological changes in disseminated sclerosis.

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[1] For full reference lists consult articles by Redlich and Stieglitz.

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